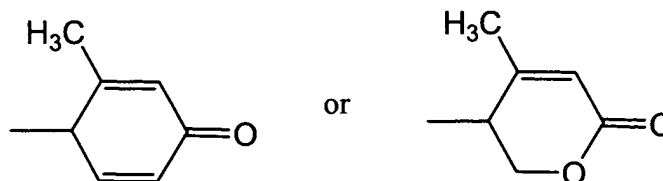


- 6 -

With regard to  $R^2$ :

$R^2$  is preferably H, but may also be a suitable substituent. Such substituents are typically and preferably alkyl or substituted alkyl. The alkyl or substituted alkyl may optionally include one or more heteroatoms which can be O, N or S, preferably N and O.

- 5 Permitted substitutions on the alkyl group are set forth above; preferred substituents include OR, where R is H or alkyl (1-6C) and =O. Also included among the preferred substituents on the alkyl group are cyclic moieties, such as piperazine, pyridine, piperidine, phenyl, and the like. Preferably, the alkyl embodiments of  $R^2$  contain 0, 1 or 2 substituents. Among preferred embodiments of  $R^2$  are included those of the formula
- 10  $-(CO)O-Y'$  wherein  $Y'$  is, for example,  $-(CH_2)_nNR_2$ , where n is an integer of 0-6 and R is as defined above; or  $Y'$  is, for example, an aliphatic or aromatic ring system, such as



- Additional illustrative embodiments of  $R^2$  include nicotinoyl and its isomers, acryloyl, and substituents of the general formula  $Y'(CH_2)_nNH(CH_2)_nCHOH(CH_2)_n-$  wherein  $Y'$  is a generic substituent such as optionally substituted alkyl, piperazinyl,
- 15 piperidinyl, cyclohexyl, phenyl or methoxy, and the like and wherein each n is independently an integer of 1-3.  $Y'$  is quite variable and can generally include any noninterfering moiety. Additional embodiments include those of the general formula  $Y'NH(CH_2)_n-CO$ , wherein  $Y'$  and n are as described above; also included are those of the general formula  $Y'(CH_2)_nNH(CH_2)_nCO$  where  $Y'$  and n are as described above; and those
- 20 of the formula  $Y'(CH_2)_nCO$  and  $Y'(CH_2)_nNHCO$ , wherein  $Y'$  and n are as defined above; and those of the formula  $R_2N(CH_2)_n-$  wherein R is alkyl (1-6C) and n is an integer of 1-3.

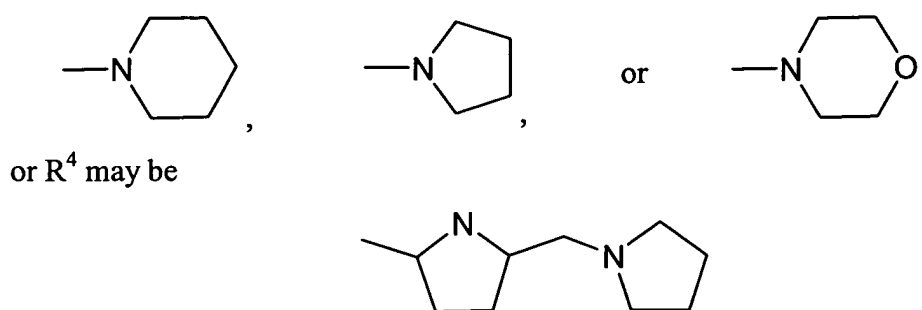
With respect to  $R^3$ :

Although  $R^3$  may be H, other embodiments are included and may be preferred. These include halo, OR,  $NR_2$ , and alkyl (1-6C), as particularly desirable.

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In embodiments wherein  $Z^1$  or  $Z^2$ , preferably  $Z^1$ , is  $CR^4$ , where  $R^4$  is other than H, preferred embodiments of  $R^4$  include those of the formula  $R_2N(CH_2)_n$ - wherein each R is independently alkyl (1-6C) or H and n is an integer of 1-6; or of the formula  $Y'(-CH_2)_n$ - wherein  $Y'$  is as defined above and n is an integer of 1-6; or those of the formula

- 5  $Y'NHCO$ ; or those of the formula  $R_2NCO$ , wherein the  $R_2$  substituents taken together form a ring which may itself be substituted, preferably by alkyl, arylalkyl, and the like. When  $R^4$  is  $Y' (CH_2)_n$ -, for example,  $Y'$  may be

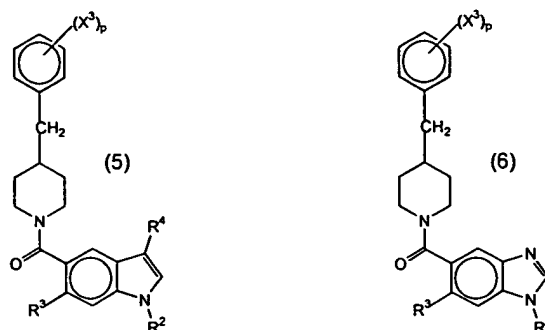


- 10 Additional illustrative embodiments of  $R^4$  include 2-, 3- and 4-pyridyl, 2-, 3- and 4-piperidyl.

- The compounds of formulas (1)-(4) may be supplied in the form of their pharmaceutically acceptable acid-addition salts including salts of inorganic acids such as hydrochloric, sulfuric, hydrobromic, or phosphoric acid or salts of organic acids such as acetic, tartaric, succinic, benzoic, salicylic, and the like. If a carboxyl moiety is present,
- 15 these compounds may also be supplied as a salt with a pharmaceutically acceptable base, including inorganic bases such as sodium hydroxide, potassium hydroxide, calcium hydroxide, ammonium hydroxide and the like or a salt with an organic base such as caffeine.

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Particularly preferred compounds of the invention are of formulas (5) and (6):



In these compounds,  $\text{R}^1$  is of the formula shown, wherein each  $\text{X}^3$  is independently halo, alkyl (1-6C), OR or  $\text{NR}_2$ , wherein R is H or alkyl (1-6C), and p is an integer of 0-3.  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^4$  are as defined above.

- 5 Also preferred are similar compounds where the positions of  $\text{R}^3$  and the illustrated embodiment of  $\text{R}^1$  are reversed; i.e.,  $\text{R}^3$  is at position 5 and  $\text{R}^1$  is in position 6.

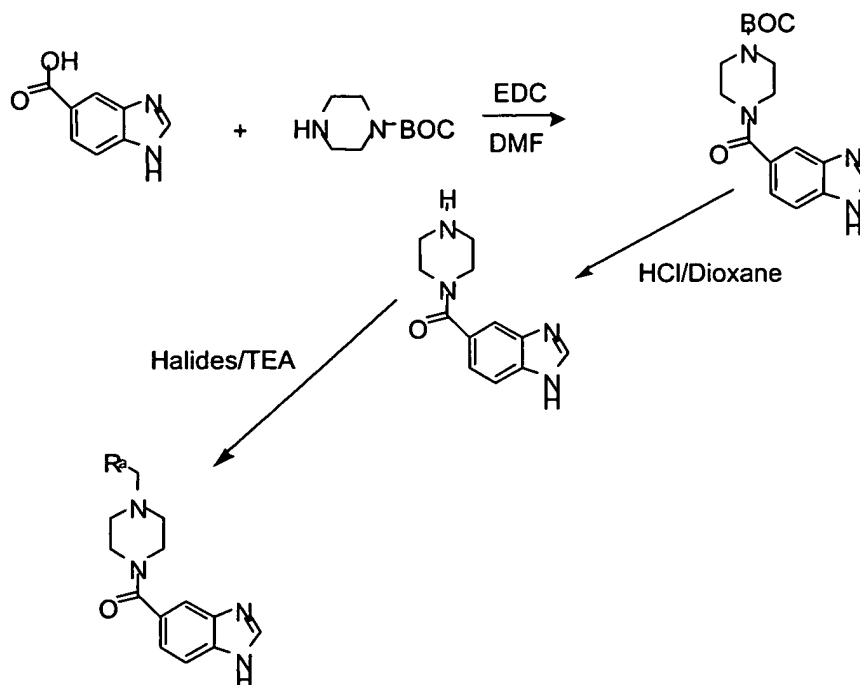
### Synthesis of the Invention Compounds

The compounds of the invention can be synthesized by a variety of methods most  
 10 of them known in the art per se. The indole, benzimidazole, or benotriazole moiety may be supplied per se and the substituent  $\text{R}^1$  coupled thereto.  $\text{R}^1$  may be supplied as such, or its synthesis may be completed when the piperazyl or piperidyl residue is already coupled to the indole, benzimidazole or benotriazole moiety. Alternatively, especially in  
 15 embodiments wherein  $\text{R}^3$  represents a non-hydrogen substituent, the appropriately substituted p-aminobenzoic acid derivative may be cyclized and then substituted with piperazine or piperidine.

Thus, for example, as shown in Reaction Scheme 1, a piperazine protected with tert-butyloxycarbonyl (BOC) is coupled to 5-carboxybenzimidazole (or 5-carboxy-indole, or 5-carboxy-benzotriazole) in a reaction mixture containing a coupling agent such as  
 20 EDAC in an inert, aprotic solvent to obtain the coupled carboxamide which is then deprotected and treated with substituted or unsubstituted benzyl halides or benzoyl halides.

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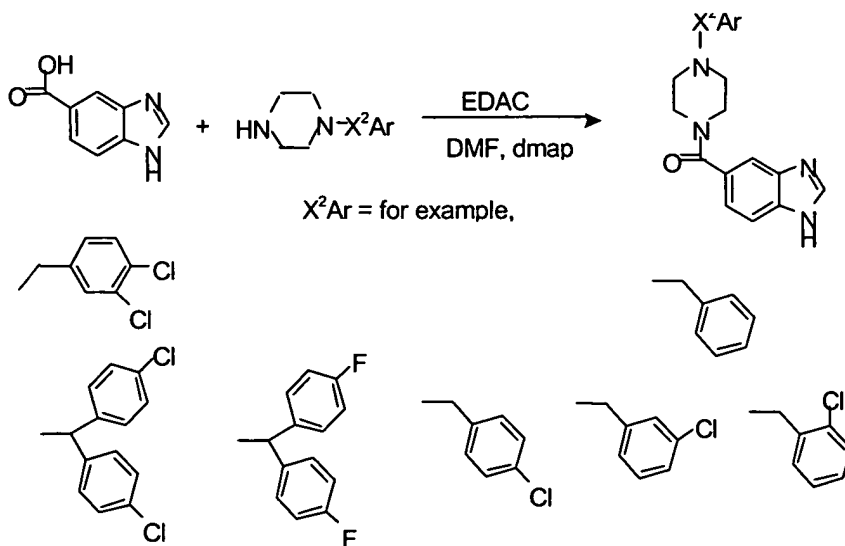
Scheme 1



R<sup>a</sup> = for example, 2,6-difluorophenyl; 3,4-difluorophenyl; 2,3-difluorophenyl; 3,5-difluorophenyl; 3-chlorophenyl; 4-chlorophenyl; 4-carboxymethylphenyl; 4-methoxyphenyl; 4-trifluoromethoxyphenyl; 4-methylphenyl; 6-chloropiperonyl; t-butylcarboxyphenyl; 3-trifluorophenyl; 2,4-dichlorophenyl; 3,4-dichlorophenyl; phenyl; methoxyphenyl; or p-tolyl.

Alternatively, as shown in Reaction Scheme 2, 5-carboxylated benzimidazole (or indole or benzotriazole) is reacted with a piperazine or piperidine moiety already substituted by X<sup>2</sup>-Ar. In this reaction, the piperazyl or piperidyl derivative is directly reacted with the carboxylated bicycloheteroatom-containing nucleus in the presence of a coupling agent such as EDAC in the presence of an inert solvent as set forth above.

### Scheme 2



In order to form the substituted piperazine required for Scheme 2, piperazine is first converted to the BOC derivative and then reacted with ArCHO in the presence of a borohydride under acidic conditions to give the substituted piperazine as shown in Reaction Scheme 3.